Survival among Women with Borderline Ovarian Tumors and Ovarian Carcinoma

A Population-Based Analysis

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BACKGROUND. Serous and mucinous ovarian tumors of low malignant potential (LMP-S and LMP-M, respectively) are noninvasive tumors that portend excellent survival when confined to the ovary. Comparison of the survival for women with LMP tumors staged as distant with women who have carcinoma may have important implications for diagnostic terminology and clinical management.

METHODS. The authors compared relative survival rates among patients diagnosed with ovarian tumors during the period 1988–1999 (with follow-up through 2000) by histologic type, disease stage, tumor grade (for carcinomas), and patient age, using data from the Surveillance, Epidemiology, and End Results Program.

RESULTS. The overall relative survival rate at 10 years (± 1.96 standard errors) was 96.9% ± 2.3% for women with LMP-S tumors, 30.4% ± 1.7% for women with serous carcinoma (CA-S); 94.0% ± 3.1% for women with LMP-M tumors, and 64.7% ± 3.4% for women with mucinous carcinoma (CA-M). The survival rate at 10 years for women with distant-stage LMP-S tumors was 89.9% ± 5.3%, compared with 96.1% ± 8.6% for women with well differentiated, localized CA-S. The survival rate for women with distant-stage LMP-M tumors at 5 years was 85.5% ± 9.0%, compared with 95.5% ± 3.4% for women with well differentiated, localized CA-M (data for 10 years were limited). Mucinous ovarian neoplasms were associated with an excess of second malignancies of the digestive tract.

CONCLUSIONS. Relative survival among women with distant-stage LMP tumors was not 100% and resembled the survival of women who had carcinoma exhibiting favorable prognostic features (localized stage). Future studies of women with high-stage LMP tumors are required to clarify the pathogenesis of extraovarian lesions and their implications for management and prognosis. ***Cancer* 2004;100: 1045–52.** *Published 2004 by the American Cancer Society.**

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Historically, the histopathologic diagnosis of *borderline* or *low malignant potential* (LMP) tumors of the ovary was created to designate neoplasms that often were associated with extraovarian disease but pursued an unexpectedly indolent course.[1–3] Although LMP tumors are rare (U.S. incidence, ≈ 2.5 per 10^5 women-years[4]), these tumors are of considerable interest because they often affect young women who must make decisions regarding the risks of fertility-sparing treatments. Recent clinicopathologic studies and reviews have suggested that a minority of the most common types of LMPs, serous LMP (LMP-S) and mucinous LMP (LMP-M), cause death.[5–13] This has prompted debate about whether the classification of ovarian tumors should be revised and whether the diagnosis of ovarian tu-

mors can be improved through use of better histopathologic criteria, the identification of prognostic markers, or other means. In response to these discussions, the National Cancer Institute sponsored a workshop to review critical issues related to LMPs.

Histologically, LMPs display neither the cytologic anaplasia nor the destructive invasive growth typical of carcinoma; however, LMP tumors (LMP-S in particular) often are associated with extraovarian lesions of unknown pathogenesis, termed *implants*.[8,10–12] Most implants resemble LMP-S tumors and portend much better survival than metastatic carcinoma. A minority of implants shows invasive growth that often proves fatal.[7,8,10–12] Some studies, conducted primarily by a single group of investigators, have suggested that LMP-S tumors that display micropapillary architecture are more likely than other LMP-S neoplasms to present with ovarian surface involvement, bilateral ovarian tumor, and implants (both noninvasive and invasive).[14,15] A proposal has been advanced to reclassify these micropapillary tumors as carcinomas and to change the designation of the remaining tumors currently in the *LMP* category to a term implying unequivocal benignity.[15] However, based on the observation that the behavior of micropapillary tumors without invasive implants is similar to that of usual LMP-S tumors, several other groups have failed to endorse the proposed changes to the terminology for ovarian tumors.[13,16–19]

Analogously, recent studies of LMP-M tumors also have prompted debate. Recent studies have revealed that pseudomyxoma peritoneii, a fatal condition resulting from intraabdominal accumulation of mucin, is related most frequently to ruptured appendiceal neoplasms, rather than to LMP-M tumors,[10–12,20,21] and that misdiagnoses of metastatic adenocarcinomas as primary ovarian mucinous neoplasms are common.[10–12,22,23]

If survival among women with LMP tumors equaled that of women of similar age and race without ovarian tumors and was much better than that of women with the most indolent carcinomas, then the elimination of the LMP diagnosis could be justified easily. A recent analysis of population-based data collected by the Surveillance, Epidemiology, and End Results (SEER) Program, focusing on treatment practices for patients with LMP tumors (without stratification by histologic type), found that the survival rate among women with Stage I LMP tumors was 97%, compared with 88% for women with Stage III tumors.[24] In the current analysis, we compared the survival of women diagnosed with LMP tumors to that of women diagnosed with carcinomas that exhibited similar differentiation (LMP-S was compared to serous carcinoma [CA-S] and LMP-M was compared to mucinous carcinoma [CA-M]). Our goal was to determine whether survival among women with unfavorable categories of LMP tumors overlapped with that of women with the most favorable categories of carcinomas. If vastly better outcomes were observed among women with LMP tumors, that would argue in favor of the replacement of *LMP* with a more benign designation. However, comparable survival data among women with LMP tumors and women with carcinoma would not favor a change in terminology. The current analysis was based on pathology reports that are broadly representative of practices throughout the United States. We did not assess survival among women based on expert histopathologic review, nor did we perform ancillary studies that might have provided insight on the pathogenesis of LMP tumors and had implications regarding the pathologic classification of these tumors.

MATERIALS AND METHODS

Case Ascertainment

The SEER Program, which is administered by the National Cancer Institute, has collected data from 9 population-based tumor registries on cases diagnosed since 1973 and from 11 registries since 1992 (recently representing approximately 14% of the United States population).[25] Reporting for LMPs began in 1988. We combined cases reported to 9 SEER registries (San Francisco-Oakland, CA; Connecticut; Detroit, MI; Hawaii; Iowa; New Mexico; Seattle, WA; Utah; and Atlanta, GA) between 1988 and 1991 and cases reported to 11 SEER registries (including Los Angeles, CA, and San Jose-Monterey, CA) between 1992 and 1999 into a single analysis. Of 26,635 total ovarian tumors diagnosed, we selected 14,699 for further analysis based on the following International Classification of Diseases for Oncology (second edition; ICD-O-2) codes[26]: LMP-S, 8442 and 8462; CA-S, 8441, 8460, and 8461; LMP-M, 8472 and 8473; and CA-M, 8470, 8471, 8480, and 8481. Ovarian tumors coded as papillary LMP, papillary carcinoma, or histologic type not specified, as well as neoplasms that were reported only on a death certificate, were excluded. Only histopathologically diagnosed tumors that represented either the only primary tumor or the first primary tumor diagnosed for each patient were included, resulting in 2817 LMP-S tumors, 8091 CA-S tumors, 1735 LMP-M tumors, and 2056 CA-M tumors for analysis.

Analysis

Vital status data were collected until death or last contact before December 2000, or until December 2000 if later follow-up information was available. For

TABLE 1
Demographic Characteristics of Patients and Stage Distribution of Ovarian Tumors[a]

	No. of patients (%)						
	Age range (yrs)			Disease stage			
Characteristic	< 40	40–54	≥ 55	Local	Regional	Distant	Unknown
Low malignant potential							
Serous (n = 2817)	1027 (36.5)	950 (33.7)	840 (29.8)	2006 (71.2)	152 (5.4)	624 (22.2)	35 (1.2)
Mucinous (n = 1735)	631 (36.4)	550 (31.7)	554 (31.9)	1567 (90.3)	38 (2.2)	109 (6.3)	21 (1.2)
Carcinoma							
Serous (n = 8091)	486 (6.0)	1961 (24.2)	5644 (69.8)	825 (10.2)	413 (5.1)	6709 (82.9)	144 (1.8)
Mucinous (n = 2056)	389 (18.9)	544 (26.5)	1123 (54.6)	1100 (53.5)	93 (4.5)	814 (39.6)	49 (2.4)

[a] Data were reported to 9 Surveillance, Epidemiology, and End Results (SEER) registries between 1988 and 1999 and to 11 SEER registries between 1991 and 1999. *Stage* refers to SEER historic Stage A.

descriptive purposes, we tabulated data on age (age $<$ 40 years, 40–54 years, or $\geq$ 55 years), race (black, white, or other), and historic Stage A (localized, regional, distant, or unstaged) for each tumor type using SEER*Stat software (National Cancer Institute, Bethesda, MD).[27] The SEER historic Stage A *localized* corresponds to International Federation of Gynecology and Obstetrics (FIGO) Stages IA and IB; the SEER *regional* stage corresponds to FIGO Stages IC, II A, IIB, and IIC; and the SEER *distant* stage corresponds to FIGO Stages III and IV. Distributions of these variables and of survival outcomes in the data sets from the group of 9 SEER registries (1988–1991) and the group of 11 registries (1992–2000) were similar, and these data were combined. Staging of LMPs was based only on histologically diagnosed extraovarian lesions (called *implants*); implants removed from undesignated sites were coded as abdominal involvement. The presence of implants increased the stage of an LMP tumor, but data on the subclassification of implants as noninvasive or invasive were unavailable. In analyses in which stage was not a stratification variable, cases lacking these data were included.

Cumulative relative survival, which estimates survival among cancer patients in the absence of competing causes of death, was calculated by tumor type, disease stage, and patient age. Specifically, this computation was used to compare the proportion of surviving patients with ovarian tumors at yearly intervals after diagnosis with women without malignant disease who resided in the same registry catchment areas and who were matched for age, race, and calendar year. A point estimate for survival with confidence limits (point estimate $\pm$ 1.96 standard errors [SE]) $\geq$ 100% would indicate survival indistinguishable from that of matched women without ovarian tumors. Data for stage-stratified tumor types were plotted on an arithmetic scale over 10 years of follow-up. We repeated these analyses for all tumor types, stratifying based on age and (for women with carcinoma) tumor grade (LMP tumors were not graded).

To assess the likelihood that cases coded as mucinous ovarian tumors represented misclassified adenocarcinomas metastatic to the ovary, we performed two indirect comparisons by histologic type of ovarian tumor: 1) the ratio of observed-to-expected (O/E) second tumors, focusing on the digestive tract, and 2) the specific competing causes (nonovarian tumor) of death. We reasoned that if second tumors of the digestive tract were in excess among women with mucinous ovarian tumors and if these second primaries were a frequent cause of death, then misclassification of metastases as ovarian mucinous tumors was likely.

RESULTS

Demographic Features of Patients and Stage Distribution of Ovarian Tumors

The age distributions of women diagnosed with LMP-S and LMP-M were similar: approximately equal percentages of women were age $<$ 40 years, ages 40–54 years, and age $\geq$ 55 years at diagnosis (Table 1). In contrast, 69.8% of CA-S tumors and 54.6% of CA-M tumors were diagnosed among women age $\geq$ 55 years. Only 6.0% of CA-S tumors were diagnosed among women age $<$ 40 years, whereas 18.9% of CA-M tumors were diagnosed among women in this age group. The greatest percentage of each tumor type was diagnosed among whites, ranging narrowly from 84.0% to 88.6% for the 4 tumor types (data not shown). Tumors staged as localized disease accounted for 71.2% of LMP-S and 90.3% of LMP-M, compared with only 10.2% of CA-S and 53.5% of CA-M. Tumors staged as distant disease accounted for 82.9% of CA-S and 39.6% of CA-M.

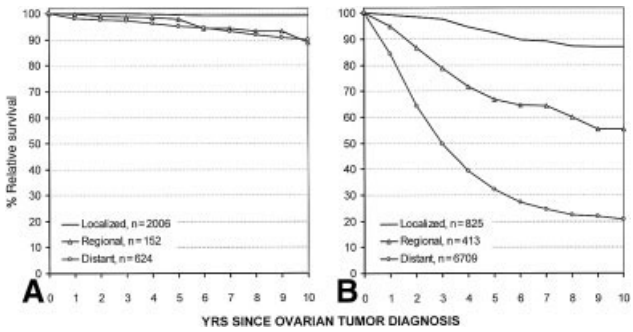

FIGURE 1. Cumulative relative survival curves for women with (A) serous tumors of low malignant potential (LMP-S) and (B) serous carcinoma (CA-S). Survival for women with LMP-S staged as localized disease remained near 100%, but for women with LMP-S tumors that were staged as regional or distant disease, survival decreased with increasing follow-up and was similar to survival data for women with localized CA-S.

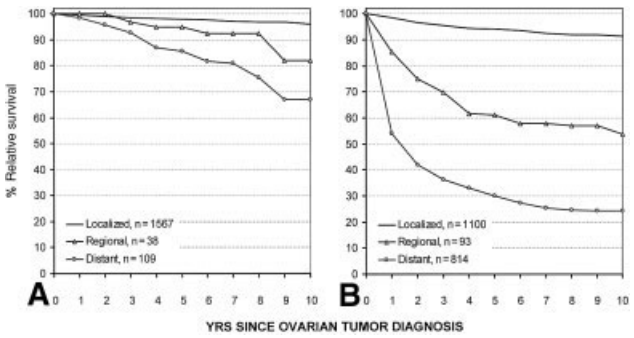

FIGURE 2. Cumulative relative survival for women with (A) mucinous tumors of low malignant potential (LMP-M) and (B) mucinous carcinoma (CA-M). Survival for women with either localized LMP-M or CA-M was $>$ 90%. Women who had regional-stage or distant-stage LMP-M fared worse compared with women who had localized CA-M.

Cumulative Relative Survival Rates among Women with Serous Tumors

The cumulative relative survival rate (± 1.96 SE) among women with LMP-S was 98.4% (± 1.1%) at 5 years and 96.9% (± 2.3%) at 10 years of follow-up, compared with 40.5% (± 1.4%) and 30.4% (± 1.7%), respectively, for women with CA-S at 5 years and 10 years of follow-up. The analysis of outcomes for LMP-S tumors staged as regional was limited by small numbers (n = 152); however, for women with LMP-S staged as distant disease, relative survival at 5 years was nearly equivalent to the corresponding rate for women with localized disease but clearly was lower with lengthier follow-up (at 10 years of follow-up: localized, 99.2% ± 2.6%; distant, 89.9% ± 5.3%) (Fig. 1). Survival among women with LMP-S staged as distant disease was similar to survival among women with CA-S staged as localized, which was associated with a survival rate of 92.3% (± 3.0%) at 5 years and 87.0% (± 5.2%) at 10 years; survival among women with CA-S staged as regional or distant disease was markedly reduced.

Survival among women with LMP-S varied minimally with age, whereas, among women with CA-S, the survival rate for the youngest women was 63.3% (± 4.8%) at 5 years, compared with only 45.5% (± 1.6%) for the oldest women (data not shown). Survival among women with CA-S continued to decline progressively with age at 10 years of follow-up. Tumor grade was an important predictor of survival for women with CA-S; well differentiated tumors were associated with a cumulative survival rate of 75.9% (± 4.8%) at 5 years and 70.9% (±7.1%) at 10 years of follow-up, with sharply decreased survival for women with all other tumor grades. Among women with well differentiated CA-S tumors that were staged as localized, survival was excellent: 96.8% (± 5.7%) at 5 years and 96.1% (± 8.6%) at 10 years. However, survival for women with well differentiated CA-S tumors that were staged as distant declined to 63.9% (± 6.6%) at 5 years and to 55.2% (± 9.3%) at 10 years. Women age $<$ 40 years with CA-S tumors that were staged as localized had similar relative survival rates.

Cumulative Relative Survival Rate among Women with Mucinous Tumors

The cumulative relative survival rate for women with LMP-M was 97.0% (± 1.5%) at 5 years and 94.0% (± 3.1%) at 10 years of follow-up, compared with 67.4% (± 2.5%) and 64.7% (± 3.4%), respectively, for women with CA-M at 5 years and 10 years of follow-up. These data reflect the fact that 90% of LMP-M tumors were localized to the ovary at presentation. CA-M staged as localized was associated with slightly lower relative survival rates: 94.1% (± 2.3%) at 5 years and 91.3% (± 4.0%) at 10 years (Fig. 2).

Follow-up data for women who had mucinous tumors that were staged as regional or distant were limited; however, the survival data for these women clearly was worse than the survival data for women who had localized tumors, with dramatic decreases for women who had CA-M tumors staged as distant and smaller reductions for women with LMP-M tumors. Survival for women who had LMP-M or CA-M staged as distant was worse than the survival data for women who had comparable tumors that were staged as regional. Survival for women with LMP-M varied little with age (data not shown), declining slightly among the oldest women after 10 years of follow-up (90.5% ± 8.4%), whereas, among women with CA-M, cumulative survival was considerably worse for older women.

TABLE 2
Causes of Nonovarian Tumor Deaths among Patients Diagnosed with Ovarian Tumors[a]

	No. of patients (%)			
Cause of death	LMP-S	CA-S	LMP-M	CA-M
Nonovarian malignancy[b]				
Digestive	5 (3.3)	35 (4.8)	15 (12.1)	43 (18.0)
Pulmonary	5 (3.3)	23 (3.1)	16 (12.9)	14 (5.9)
Other	16 (10.7)	206 (28.0)	15 (12.1)	53 (22.2)
Total	26 (17.3)	264 (35.9)	46 (37.1)	110 (46.0)
Nonneoplastic	109 (72.7)	343 (46.7)	71 (57.3)	104 (43.5)
Unknown	15 (10.0)	128 (17.4)	7 (5.6)	25 (10.5)
Total	150 (100)	735 (100)	124 (100)	239 (100)

LMP: low malignant potential (borderline tumor); LMP-S: serous tumor of low malignant potential; CA-S: invasive serous carcinoma; LMP-M: mucinous tumor of low malignant potential; CA-M: invasive mucinous carcinoma.

[a] Data were reported to 9 Surveillance, Epidemiology, and End Results (SEER) registries between 1988 and 1999 and to 11 SEER registries between 1991 and 1999. Percentages refer to columns.

[b] Digestive system tumors included tumors of the esophagus, stomach, small and large intestine, rectum, pancreas, biliary tract, and other digestive organs. Eight women whose coded cause of death was a tumor classified as in situ, benign, or unknown behavior (LMP-S in one woman, CA-S in five women, and CA-M in two women) were included within the category of deaths not related to ovarian malignancy.

For women with well differentiated CA-M tumors, the survival rate was 85.7% (± 3.8%) at 5 years and 79.8% (± 6.5%) at 10 years; survival was worse for women with moderately differentiated tumors and fell drastically for women with other tumor grades.

Among women with CA-M tumors, well differentiated localized neoplasms were associated with cumulative survival at 5 years of follow-up of 95.5% ± 3.4%, which decreased slightly at 10 years, to 89.7% ± 7.1%. Survival for women with localized CA-M tumors was similar, irrespective of age.

Frequency of Nonovarian Tumor Deaths among Women Diagnosed with Ovarian Tumors of Low Malignant Potential and Carcinomas

Among women who did not die of ovarian tumors, deaths from nonovarian malignancies occurred more frequently among patients with CA-S and CA-M than among those with LMP-S and LMP-M (Table 2). Women with mucinous tumors were diagnosed with a significant excess of digestive tract carcinomas (LMP-M: O/E = 2.1.; confidence bounds, 1.3–3.2; CA-M: O/E = 2.7; confidence bounds, 1.9–3.7), and these second malignancies were an important, competing cause of death. Women with serous tumors did not experience a similar excess of digestive tract malignancies (LMP-S: O/E = 1.5; confidence bounds, 1.0–2.3; CA-S: O/E = 1.0; confidence bounds, 0.8–1.4). Among women with mucinous neoplasms (especially LMP-M tumors) relative to women with serous tumors, fatal pulmonary malignancies accounted for a greater percentage of deaths related to competing causes. Deaths ascribed to uterine corpus malignancies (n = 23 [4.8%]) and to tumors of the peritoneum, omentum, and mesentery (n = 31 [4.2%]) represented a more common competing cause of death among women who had serous tumors compared with women who had mucinous neoplasms.

DISCUSSION

In the current analysis, the cumulative relative survival rate for women with LMP-S tumors staged as localized remained close to 100%; however, for women with distant disease, survival was reduced (≈ 90%) relative to tumor-free women, especially at 10 years of follow-up. Among women with LMP-S, age was associated with reduced survival only among the oldest patients with distant-stage disease, as reported previously.[28] The results of our survival analysis were similar to the results from a recent analysis of SEER data that did not specify histologic type[24] and from an exhaustive review of the clinical literature on LMP-S tumors.[7] These data suggest that LMP-S tumors localized to the ovary portend a benign outcome, although some women with distant disease die of their tumors. Therefore, these findings do not support a decision to replace the existing LMP terminology with a benign term. However, research establishing that the pathogenesis of fatal extraovarian LMP-S tumors reflects a process distinct from that related to the development of their associated ovarian primaries may provide such evidence in the future.

Increasingly, data suggest that deaths among women with LMP-S are caused by foci of peritoneal tumor that resemble invasive, low-grade, serous carcinoma rather than LMP-S. Therefore, deaths among women with LMP-S may be caused by implants that undergo malignant transformation at extraovarian sites, sometimes after years of dormancy, or by the development of independent primary peritoneal tumors, which are indistinguishable from ovarian serous carcinoma. Molecular data obtained to determine whether primary ovarian tumor tissue and implants in women with LMP-S share the same clonal lineage are conflicting.[29–33] Resolution of this question would have potentially important implications for the classification of ovarian tumors and the designation of their associated extraovarian lesions as metastases, as concurrent primary tumors, or perhaps as something else akin to endometriosis, a benign lesion with potential for malignant transformation.

The epidemiology of LMP tumors has been studied and reviewed,[34,35] but findings have been incon-

sistent. Analyses specifically focused on LMP-S tumors associated with extraovarian disease are needed to determine risk factors for spread and for malignant transformation. Although it has been established that survival is worse for women who have invasive implants compared with women who have noninvasive implants, different criteria for invasion have been proposed, and interobserver reproducibility data, especially among practicing community pathologists, are lacking.[7,36,37] Finally, the behavior of serous tumors that show micropapillary growth without destructive invasion should be compared with a large representative set of LMP tumors that lack micropapillae, including tumors that demonstrate ovarian surface involvement and/or bilaterality. Many prognostic features of LMP-S tumors are correlated; a multivariate analysis will be required to determine which features have independent predictive value.

Survival rates for women with both localized LMP-M and CA-M were excellent, exceeding 90% at 10 years for both tumor types. Survival clearly decreased for women with LMP-M tumors associated with extraovarian disease; however, such tumors constituted $< 10\%$ of the total, resulting in less precise estimates. Nonetheless, the survival of women who had LMP-M with regional or distant-stage disease was better than the survival of women with comparably staged CA-M. Survival for patients with CA-M declined with both increased disease stage and older age.

Recognition that grading has important prognostic value in assessing both CA-S and CA-M tumors indicates that a refined, reproducible, and standardized grading system for ovarian carcinoma is needed.[38,39] The development of improved techniques for early detection and staging also are an obvious priority given the tremendous impact of disease stage on survival for all ovarian tumors.[40] A recent multicenter study of 52 Stage I invasive carcinomas (mostly serous) found an estimated actuarial survival rate of 93% at 10 years and that 71% of women who had attempted to become pregnant conceived.[41]

Clinicopathologic studies have demonstrated that metastatic adenocarcinomas often present as ovarian masses that are misdiagnosed as primary ovarian mucinous tumors.[10–12,22,23] It also has been established that most, and perhaps all, cases of pseudomyxoma peritonei are caused by ruptured appendiceal neoplasms rather than ovarian tumors.[10–12,20,21] Women with pseudomyxoma may have glandular deposits in their ovaries derived from an appendiceal neoplasm that mimics a primary mucinous ovarian tumor. Metastatic adenocarcinomas or pseudomyxomas misclassified as primary mucinous ovarian tumors would spuriously reduce the estimated survival of patients with these ovarian neoplasms.

The current analysis could not directly assess whether ovarian tumors that were classified as mucinous represented misdiagnoses of metastases to the ovaries. However, we did find that tumors coded as ovarian mucinous neoplasms were associated with an excess of second tumors of the digestive tract and that gastrointestinal tumors also accounted for a relatively high percentage of competing causes of death. Therefore, we suspect that some fatalities ascribed to LMP-M and CA-M may have been caused by metastatic adenocarcinomas or pseudomyxoma of appendiceal origin that occurred among women who never had an ovarian primary tumor. This raises concerns that analyses of risk factors for mucinous tumors may have been affected by the misclassification of tumors.[42–47] The reported association between smoking and mucinous neoplasms is interesting in light of the relatively high frequency of deaths from pulmonary carcinomas among women with LMP-M.[42,46,47]

The strengths of this study included the large number of tumors analyzed, the inclusion of patients highly representative of the general U.S. population (as opposed to referral practices), and the ability to compare the survival of women with ovarian tumors with that of a population matched with respect to age, race, and calendar year. However, we were unable to review pathology slides; therefore, we could not assess the type of implant (noninvasive or invasive), the presence of micropapillary features in LMP-S tumors, the possible misdiagnosis of metastases as primary ovarian mucinous neoplasms, and other pathologic features. We also could not evaluate the mechanisms of death among women with ovarian tumors; specifically, we were unable to determine whether deaths were caused by carcinomatosis, nonneoplastic adhesions, or other mechanisms. Nonetheless, our data have identified subgroups of women with serous and mucinous ovarian tumors who have extremely good survival, providing population-based evidence to indicate that the presence of extraovarian lesions and, by implication, the nature of these lesions represent the pivotal prognostic factors. Because LMPs will no longer will be reported to the SEER Program, the development of a registry with access to pathologic material should be considered, and additional molecular studies of pathogenesis should be encouraged.

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